REMARKS

Amendments

The cross-references section is updated herein to reference the provisional application number (which is now available) and the issued parent patent. A substitute declaration, including the provisional application and parent patent Nos., is submitted herewith.

In order to expedite prosecution, claim 43 is incorporated into claim 42 and hence is canceled as moot. Claim 44 is amended so as to depend on claim 42 due to the cancellation of claim 43.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

The Outstanding Rejection

The only rejection in the case is a rejection of claims 42-49 under 35 USC Section 112, first paragraph. In the Examiner's view, the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants submit that the invention set forth in claims 42 and 44-49 herein is enabled by the specification.

The Present Invention

Claim 42 herein is directed to a method for treating cancer characterized by overexpression of HER2 receptor in a mammal comprising administering to the mammal subcutaneously a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor in an amount of about 50mg/mL to about 400mg/mL. Claim 47 is concerned with a method for treating a mammal comprising administering a therapeutically effective amount of a stable reconstituted formulation to the mammal in order to treat cancer characterized by overexpression

of HER2 receptor in the mammal, wherein the reconstituted formulation comprises an antibody which binds HER2 receptor in an amount of about 50 mg/mL to about 400mg/mL and has been prepared by reconstituting a lyophilized mixture of the antibody and a lyoprotectant in a diluent, wherein the antibody concentration in the reconstituted formulation is about 2-40 times greater than the antibody concentration in the mixture before lyophilization.

Applicants will demonstrate that the claimed invention is enabled by the present application.

The present application describes the HER2 receptor antigen and antibodies that bind to it (pages 9 and 25, for example). Moreover, the specification provides guidance as to the production of other antibodies that bind to HER2 receptor (pages 13-19), and explains how those antibodies can be used in therapeutic methods (page 24, lines 11-16). At the time of filing the present application, therapeutically active anti-HER2 antibodies had been described in the patent and scientific literature. See, *e.g.* WO92/22653 referenced on page 25 of the application and corresponding to US Patent Nos. 5,821,337 and 6,054,297 to Drs. Carter & Presta; all of record. Aside from the Carter & Presta patent publication specifically referenced in the present specification, the art at the time of filing taught therapeutically useful anti-HER2 antibodies (see, *e.g.* WO89/06692, corresponding to US Patent Nos. 5,677,171, 5,725,856, 5,772,997, and 6,165,464, all of record; as well as Hudziak *et al. Mol. & Cell. Biol.* 9(3):1165-1172 (1989); and Fendly *et al. Cancer Research* 50:1550-1558 (1990); also both of record). Those patent and scientific publications describe antibodies such as 4D5, 3E8, 3H4, 7C2, 2C4, 7F3 etc that displayed therapeutic efficacy in pre-clinical experiments. Hence, Applicants submit that the disclosure of the present application, combined with the art at the time of filing, does enable therapeutically active anti-HER2 antibodies other than the exemplified huMAb4D5-8 antibody.

The specification further describes how to make a formulation comprising

the anti-HER2 antibody in an amount of about 50mg/mL to about 400mg/mL (see parent patent; US Patent No. 6,267,958, submitted herewith).

Finally, the instant application describes how the formulation can be administered subcutaneously to a mammal to treat cancer characterized by overexpression of HER2 receptor in the mammal (pages 23-24). See, also, Combs *et al.* (1999) (of record), concerning subcutaneous administration of a formulation comprising an anti-HER2 antibody according to the teachings in the present application.

Hence, Applicants submit that the presently claimed methods are enabled.

Applicants' Response to the Examiner's Bases for Maintaining the Rejection

Applicants turn now to the Examiner's bases for maintaining the rejection. With respect to the Examiner's suggestion that there is "no teaching disclosed in the specification of treating or inhibiting the growth of tumor cells", or of "properties of an anti-HER2 antibody that would have therapeutic efficacy," Applicants explain above where such teaching can be found and further rely on the art at the time of filing as supplementing the disclosure concerning therapeutically effective anti-HER2 antibodies. The patent "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fe. Cir. 1986). Applicants submit that, when the present application was filed in 1995, therapeutically active anti-HER2 antibodies were well known in the art and supported by the instant specification, as evidenced by the discussion above.

Addressing the Examiner's contention that the application is "totally focused on an optimal formulation, which has no support in the specification as to superior treatment or unexpectedly better results," Applicants point out that the present application describes the benefits of the present invention at pages 2-4 for example. In any event, Applicants submit that superior treatment or unexpectedly better results

need not be demonstrated to show that the presently claimed method is enabled - the Examiner has advanced no rationale for requiring a showing of superior treatment or unexpected results with respect to the invention set forth herein.

The Examiner questions whether the studies relied upon in the previous amendment provide support for the presently claimed method on the basis that "several antibodies were demonstrated to bind *in vitro* to transfected tumor cells" and "the *in vivo* experiments with 2H11 and 3E8 were also directed to inhibiting transfected tumor cells and not spontaneously occurring cancers overexpressing HER-2."

First, Applicants point out that the *in vitro* studies relied upon by Applicants were indeed performed with spontaneously occurring cancer cells overexpressing HER-2 (*i.e.* SK-BR-3 cells obtained from an actual human breast tumor), rather than "transfected tumor cells" as the Examiner suggests (see Fig. 3 of the '856 patent and Table 1 of Hudziak *et al.* (1989)).

Second, in relation to the *in vivo* data (in the '856 patent and Combs *et al.* (1999)), Applicants point out that those preclinical models have been shown to be predictive as to the efficacy of an anti-HER2 antibody formulation in patients (compare the studies in the '856 patent with the proven efficacy of the HERCEPTIN® drug as evidenced in the (Trastuzumab) Product Information (2000), both of record).

Therefore, Applicants submit that the preclinical data can be relied upon in support of the claims herein to treating a mammal with the formulation.

Finally, the Examiner argues that the data in Combs *et al.* "can be considered to provide support for a very specific MAb with a very specific formulation characteristic, and as a formulation for subcutaneous use in treatment of cancers overexpressing HER-2."

Applicants submit that the data in Combs *et al.* further supports the enablement of the presently claimed invention. In particular, Applicants have demonstrated above that the present application, in combination with the art at the time of filing, enabled the presently claimed formulation with a genus of anti-HER2 antibodies, treating cancer characterized by overexpression of HER2 receptor with a formulation comprising an anti-HER2 antibody, and Combs *et al.* shows that subcutaneous administration of a formulation comprising an anti-HER2 antibody as taught in the present application works. Hence, Applicants submit that they have met their burden of showing that the present claims are enabled by the specification at the time of filing. The Examiner has not presented any *evidence* to demonstrate that the *in vivo* data with the antibody in Combs *et al.* could not be extrapolated to other antibodies. In that Applicants have demonstrated above that the specification enables the presently claimed method with a genus of therapeutically effective anti-HER2 antibodies, Applicants submit that this basis of the rejection is fully addressed.

Since, as shown above, the specification enables the presently claimed method, Applicants submit that the outstanding rejection should be reconsidered and withdrawn.

Information Disclosure Statements

Applicants do not have fully initialed PTO-1449 forms confirming that the following art has been considered:

IDS filed 7/14/99, ref nos. 59 and 60 were not initialed

IDS filed 12/27/99, ref. nos. 190-247 were not initialed

IDS filed 2/28/01, ref. no. 248 was not initialed

Applicants would appreciate it if copies of initialed PTO-1449 forms could be returned, confirming consideration of this art with respect to the present application.

A further supplemental IDS is submitted herewith.

Applicants believe that this application is now in order for allowance, and look forward to early notification to that effect. If there are however outstanding issues to be resolved, the Examiner is invited to call the undersigned to discuss those.

Respectfully submitted,
GENENTECH, INC.

Date: May 21, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the paragraph on page 1, starting at line 7 with the following:

(Twice amended) This is a divisional of application serial number 08/615,369 filed March 14, 1996 (now US Patent No. 6,267,958) which claims priority under §119(e)(1) to provisional application number [_____] 60/029,182 filed July 27, 1995, both incorporated herein by reference.

IN THE CLAIMS:

Please amend the following claims.

42. (Amended) A method for treating cancer characterized by overexpression of HER2 receptor in a mammal comprising administering to the mammal subcutaneously a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor in an amount of about 50mg/mL to about 400mg/mL [to the mammal].

44. (Amended) The method of claim [43] 42 wherein the formulation has been prepared by reconstituting lyophilized antibody in a diluent.

Please cancel claim 43 without prejudice or disclaimer.